er 'in vitro' $\beta_1$-adrenoreceptor blocking potency than practolol[12], was less active than this latter in antagonizing IIT, could be attributed to the extensive hepatic metabolism (first pass effect) which propranolol but not practolol undergoes following a single oral dose[13]. Our 'in vivo' procedure supplemented by the 'in vitro' determination of $\beta_1$-adrenoreceptor blocking potency could provide useful information on the pharmacokinetic profile of a new drug.


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## A microvolume molecular filter


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*Summary.* A microvolume polymer membrane filter based on Amicon hollow fibers is described which permits separation of low molecular weight compounds from proteins, and can be used for desalting volumes of 100 µl or less, or to separate cellular protein debris from perfusates during release studies. The filter has the advantage of being reusable and having almost no void volume.


During a recent research project, in which we were investigating neurotransmitter release from brain slices[1], it became necessary to separate the amino acid containing perfusate from proteins and cellular debris prior to analysis. Conventional Swinney type filters could not be used because of the small volume of fluid involved, 50–150 µl and centrifugation was also unsuitable.

A series of small diameter tubular polymer filter elements, 'hollow fibers' are made by the Amicon Corporation[2]. These have tightly controlled pore sizes and are available with molecular cut-offs from between 2000 to 100,000 mol.wt (as estimated for globular proteins), and are available as loose fibres (for use as artificial blood vessels etc.). They are intended to be filled, under pressure, with the solution to be filtered, the filtrate passing through the walls and the higher molecular weight substances being retained in the lumen. Thus they appeared to be eminently suited to our purpose.

The filter is constructed as depicted in the figure. A 2.5 cm length of filter element (0.5 mm i.d.), is cut off and a small amount of cyanoacrylate cement applied to one end to seal it off. A disposable 27G (0.47 mm o.d.) hypodermic needle is cut to 0.5 cm length (by filing a nick and breaking off the excess) and the end filed smooth. It is important not to use

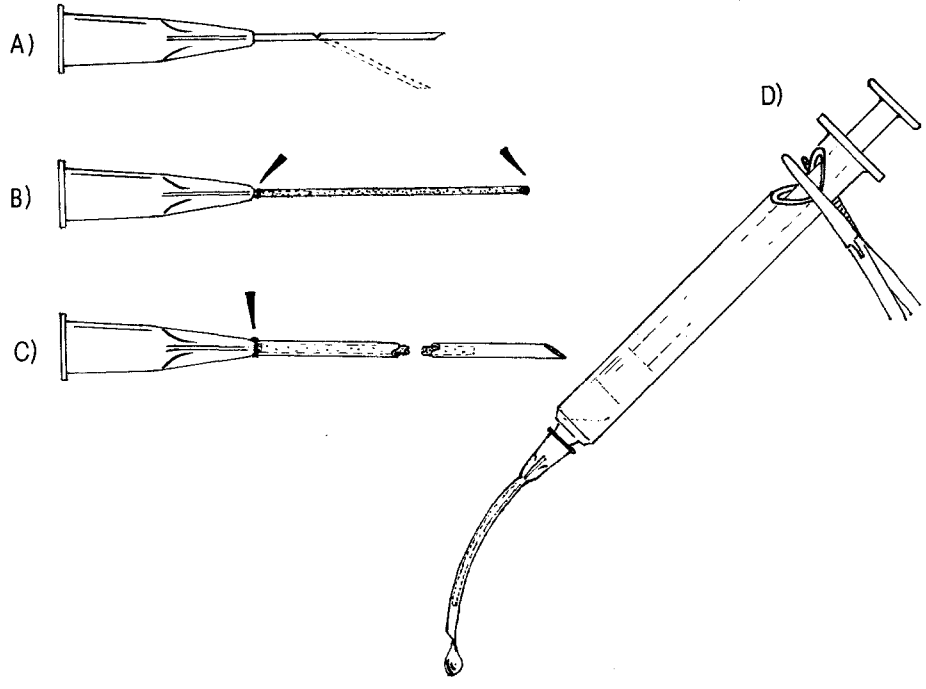


Figure. Stages in the assembly of a microvolume filter. A) the hypodermic needle is cut to length by filling a nick in the tube and bending the excess off, after which the cut end should be smoothed with a file. B) a length of filter element is slipped over the cut needle and a drop of cement used to glue it to the base of the needle and to block the end (arrows). C) polyethelene tubing is then slid over the element and affixed to the base of the needle with cement. D) modifications that can be made to a 1-ml tuberculin syringe to permit it to be used as a combined pressure source and reservoir. The inside edges of the aperture at the top of the syringe should be smoothed, otherwise the rubber seal of the plunger will be damaged. Any suitable haemostat forceps can be used to clamp the plunger in place.

disposable needles which have an aluminium insert, if the filter is to be reused, since electrolyte solutions will cause corrosion and hence contaminate the filter.

The needle is slipped into the open end of the filter and cyanoacrylate cement used to secure it. Next a 4 cm length of 1.2 mm i.d. nylon or polyethylene catheter tubing is cut, one end tapered and the other roughened slightly, slipped over the filter element and secured with cyanoacrylate cement. Since the filter requires considerable driving pressure, this tube serves to prevent rupture of the element and to channel fluid flow. Once the filters have been wetted they must be stored wet to retain their properties.

The filters are intended for use with driving pressures of up to 2 atm maximum. Where a large number of filtrations need to be carried out simultaneously, a pressure manifold having adapters for the hypodermic needles can be constructed and the driving pressure obtained from a regulated compressed gas source. For one-off filtrations, the modified hypodermic syringe shown in figure b, is sufficient, the inner edges of the hole being smoothed to permit the plunger to be removed and reinserted without damage. A pair of haemostat forceps is used to clamp the plunger in place during filtration. This approach takes advantage of Boyle Mariotte's Law: $P_1V_1 = P_2V_2$; each halving of the air volume doubles the pressure. Thus it is a simple matter to insert 100 µl or so of solution through the side hole, shake it down to the filter tip, insert the plunger and compress the air space to 0.75 the original volume (giving a pressure of 1.5 atm), clamping it in place with the haemostats.

When filtration is complete, air will be forced through the membrane and this clears the filtrate out of the plastic tube. The filter can be reused in its entirety, or the membrane dissolved in scintillation cocktail or whatever, should this be required, and the needle and outer tube reused.

In order to reuse the entire filter, it must be back-flushed with solvent to clear the lumen, using a 2nd hypodermic syringe attached by an 18 G (1.28 mm) needle to the lower open end of the filter assembly. Sometimes it helps to agitate it, while back-flushing, in an ultrasonic cleaning bath, if the retained substances are difficult to remove.

1 H.J. Spencer, G. Tominez and B. Halpern, Brain Res. *212,* 194 (1981).

2 Amicon Scientific Systems Division. 21 Hartwell Avenue, Lexington (Mass. 02173, USA).

3 These fibers are available as 'loose hollow fibers' with MW cut-offs of 5000, 10,000, 50,000, 100,000 dalton, 0.5 mm lumen diameter and 2000 dalton with lumen diameter of 1.1 mm.

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